Lesser known mycobacteria

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There has been a great upsurge of interest in tuberculosis in recent years and in the association of mycobacteria, especially *Mycobacterium tuberculosis*, *M avium* and *M kansasii*, with HIV infection and the acquired immunodeficiency syndrome (AIDS). Other mycobacteria, however, also continue to cause problems, both for immunocompromised and immunocompetent patients. This article reviews present knowledge of the pathogenicity of some of these "lesser known" mycobacteria. Those that specifically relate to tropical climates (for example, *M leprae*, *M ulcerans*) are not considered. Similarly, the possible pathogenic role of *M paratuberculosis* in inflammatory bowel disease and the role of *M bovis*, especially in Africa, merit separate reviews.

Mycobacteria are identified on the basis of colonial morphology and biochemical tests including niacin production, temperature and oxygen preferences, pigment production and Tween hydrolysis. Other specialised tests include thin layer chromatography of mycobacterial lipids and, increasingly, the use of DNA probes.

M chelonae

M chelonae, sometimes called (with *M fortuitum*) the cold blooded tubercle bacillus, was originally isolated from a turtle.¹ It is often associated with cases of inoculation mycobacterioses² and has recently been described as a cause of keratitis.¹ (In the review of the literature associated with the above report, the authors found at least 14 cases of keratitis or corneal ulcer due to *M chelonae*.) It can be associated with disseminated infections,³ often in immunocompromised patients, as well as localised pulmonary infection⁴ and skin and soft tissue infections.^{5,6} It is Gram positive, but may be weakly acid fast and can be easily mistaken for *Nocardia* spp. Khooshabeh *et al*² give a useful table of differentiating features between *M chelonae* and *N asteroides* which include resistance to netilmycin and growth on Sabouraud agar as important characteristics of *M chelonae*. For a good recent review of the clinical features and treatment of infections due to these organisms, the reader is referred to the paper by McFarland and Kuritzkes.⁷

M fortuitum is often isolated as a "contaminant", hence its name, but it has been associated with disease in humans, including peritonitis in patients undergoing continuous ambulatory peritoneal dialysis,⁸ catheter related infections in patients with cancer⁹ and disseminated infection.³ It can also cause keratitis or corneal ulcers that are usually less severe than cases caused by *M chelonae*.⁷ *M chelonae* and *M fortuitum* are often resistant to standard

antimycobacterial drugs and eradication of the infection may be difficult even after surgical removal of infected tissues. Although there are no agreed therapeutic regimens for the treatment of such infections, the newer macrolides and the quinolones¹⁰ may offer promise. Several authors^{7,10} have stressed the value of reliable susceptibility testing results in guiding therapy. Removal of intravenous catheters is obviously important in catheter related infections.

Both *M chelonae* and *M fortuitum* have been isolated from renal dialysis circuits, being associated with disseminated lesions in a patient undergoing dialysis.¹¹

M shimoidei and *Mycobacterium celatum*

Brander *et al*¹² collected 14 strains of a group of slow growing mycobacteria from respiratory samples. All of the strains showed some features of *M xenopi*, *M avium* complex (MAC) and *M shimoidei*, but had a distinctive glycolipid pattern. They were recently given the species name *Mycobacterium celatum*.¹³ The organism grows relatively easily on solid media and in the Bactec radiometric system giving results similar to *M avium* on biochemical testing, but shows a mycolic acid pattern similar to *M xenopi*. The organism can be separated into two types (1 and 2) by restriction fragment length polymorphism (RFLP) analysis. Interestingly, and importantly for reference centres, *M celatum* type 1 cross-reacts with a genetic probe for the *M tuberculosis* complex (Accuprobe; Gen-probe Inc).¹⁴ The organism has been isolated from sputum or bronchial secretions from a few patients, mostly without evidence of disease, so that its general pathogenic potential is unknown. It has also been isolated from the blood of a patient with AIDS¹⁵ and more recently from a cervical lymph node in an immunocompetent infant.¹⁶ There is little information on its susceptibility to antimycobacterial agents; the isolate from the patient with AIDS, although resistant to rifampicin, was sensitive to clarithromycin and the test quinolones.¹⁵

M shimoidei itself¹⁷ is a recently described slow growing mycobacterium isolated from the respiratory tract, with some similarities to *M malmoeense* and *M haemophilum* (see later), but with some unique features (for example, growth at 45°C, positive acid phosphatase). Little is known of its pathogenicity.

M xenopi

M xenopi was first isolated from a South American toad.¹⁸ It is a slow growing mycobacterium, which grows best at 37°C and can

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colonise water supplies and cause false positive results in rinsed specimen containers.¹⁹ It can occasionally cause opportunistic disease. This organism is sometimes isolated from the respiratory tract but its pathogenicity is difficult to assess.⁴

M smegmatis

This organism is often believed to be a frequent contaminant of urinary samples. Our experience in Edinburgh is in line with the findings of Grange and Yates²⁰ that the organism is very rarely encountered in this context. (They found that out of a total of 1392 mycobacterial isolates from the genitourinary tract, collected between 1980 and 1989, only six belonged to the *M smegmatis*/*M phlei* group.) It is seldom associated with human disease, but has been described as a cause of skin and soft tissue infections.²¹

M gordonae

M gordonae is a well established contaminant of piped water supplies and in hospitals can cause contamination of microscope slides or pathological specimens with resultant false positive smears. We have had recent experience of a similar finding in relation to contamination of bronchoscopes. (The subject of mycobacteria in water supplies is well reviewed by Collins *et al.*¹⁹) It is sometimes isolated from the respiratory tract, but its pathogenic potential is doubtful. Nevertheless, Weinberger *et al.*,²² in describing a case of disseminated infection due to the organism in an 11 year old girl with renal failure, found a total of 23 additional cases in the literature, involving both disseminated and localised infections (mainly respiratory tract and soft tissues). Their plea that "*M gordonae* should not be automatically dismissed as a contaminant when isolated from clinical material" illustrates well the difficulties in assessing the significance of these organisms.

M simiae

M simiae is a slow growing mycobacterium resembling MAC but with a distinctive biochemical profile. It grows at 37°C and is a weak photochromogen. Genetically, the organism resembles *M genavense*, but unlike that organism grows readily on solid media. Although originally associated with monkeys, it has been frequently isolated from clinical samples, especially in Israel. Levy and Yoshpe-Purer, in reviewing the isolation of the organism from clinical samples,²³ were cautious about its pathogenicity, suggesting that often it may merely colonise already damaged lungs, but there is evidence that on occasion it can cause disseminated infection (sometimes jointly with MAC) in patients with AIDS.^{24,25} Most strains that have been tested have proved to be resistant to standard antimycobacterial agents, but little is known of their susceptibility to newer agents, although both clarithromycin and ofloxacin were active against *M simiae* isolates in a murine

model of disseminated infection.²⁶ There is a lack of data about treatment of human infections.

M marinum

This organism, which grows optimally at 30°C, is a recognised cause of granulomatous skin infections, especially associated with fish handlers or others working in wet environments. In his review of the literature, Edelstein²⁷ noted that while in 90% of cases the upper limb was affected, usually with granulomata, lymphatic or local spread was seen in 81% of patients. In a few patients, the infection can progress to joint infection²⁸; these infections are often diagnosed only after other more likely causes have been excluded. They respond slowly to treatment, which is usually based on local policies rather than any clinical trials. Edelstein²⁷ found that ethambutol with rifampicin was more effective than minocycline; we have found in Edinburgh that the inclusion of ciprofloxacin in treatment regimen appears to be effective. It may be that newer quinolones are more active.²⁸

M malmoense

This is a very slow growing organism, often requiring up to 12 weeks incubation on egg media but growing more rapidly in the Bactec radiometric system.^{29,30} *M malmoense* was first described as a respiratory pathogen in 1977.³¹ Since then, it has been confirmed as a respiratory pathogen that often occurs in patients with pre-existing lung disease,³²⁻³⁴ causing a chronic infection that may be clinically indistinguishable from tuberculosis. In Edinburgh, we have also noted that the organism can cause a rapidly progressive lung disease, analogous to tuberculosis, in patients with no pre-existing lung disease (Crompton, personal communication) and that it may be isolated from a variety of extrapulmonary sites including cervical lymph nodes, the urinary tract, the mouth, and bone. Disseminated disease and chronic skin sepsis have both been associated with the organism, usually in patients with underlying disease, often malignancy.³⁵⁻³⁷

Henriques *et al.*,³⁵ in their review of 221 cases, noted that the organism was isolated from the respiratory tract in 171 patients, from cervical lymph nodes in 36 and from other sites in 10 (including urine, bone marrow and skin). (In six patients the original origin of the isolate was not known.) Many patients had underlying disease, but they too noted that pulmonary disease due to *M malmoense* could develop in previously healthy patients.

Little is known about the source of the organism; it is presumed to be, like many other mycobacteria, present "in the environment", but there is no detailed information available. In Edinburgh, we have some preliminary evidence of "clustering" of cases in certain geographical areas, but more data are required.

Interestingly, the organism is very seldom reported in HIV infected patients.³⁸ In Scotland, where the organism accounts for about 30% of all atypical mycobacterial isolates, we

only know of one clinically significant isolation from a HIV positive patient.³⁹

In a review of treatment and response in pulmonary infection with *M malmoense*, Banks *et al*⁴⁰ found that the best response was given in patients who received standard antimycobacterial therapy for at least 18 months. Ethambutol seemed to be an important component.

Fastidious mycobacteria

M haemophilum

This organism was first described in 1978.⁴¹ It is a slow growing mycobacterium that requires an iron source (haemin or ferric ammonium citrate), together with incubation at 30°C, for optimum growth. The organism can cause generalised infection, with severe infection of a variety of organs including skin, respiratory tract and bone. Such infections usually occur in immunocompromised patients, including but not only patients with AIDS.⁴² A report in 1992, however, documented five cases of perihilar or cervical lymphadenitis in children who were apparently immunologically competent.⁴³ Thus this organism should be borne in mind in all cases of "film positive, culture negative" mycobacterioses, including those in non-immunocompromised patients. Appropriate, iron containing media and incubation at 30°C should be included in the culture procedures for such cases.

The source of the organism is not known, but it may be associated with water.⁴⁴ In a recent study by Yakrus and Strauss,⁴⁵ several distinct types were detected by pulsed field electrophoresis: this should help with investigations into the epidemiology of the organism. Until recently, most cases were treated empirically; the demanding nature of the organism made sensitivity testing very difficult. However, a recent report⁴⁶ gave details of a microtitre tray method utilising Middlebrook 7H9 both with added haemin and incubated at 30°C for 10 days. The authors tested 17 isolates and found that while most were resistant to ethambutol and cotrimaxazole and moderately resistant to isoniazid, most strains were inhibited by quinolones, the newer macrolides (especially clarithromycin) and the rifamycins, including rifampicin and rifabutin, were active. The optimum duration of therapy and number of agents required remain to be established by proper clinical trials; reports in the literature cite courses ranging from a few weeks to several months.

M genavense

Several authors have described the isolation of mycobacteria which, while growing in Bactec radiometric vials, were difficult or impossible to subculture or to grow on solid media. Hirschel *et al*⁴⁷ described fatal infection with a novel mycobacterium that was seen in post-mortem smears, grew in the Bactec from several postmortem tissue homogenates, but could not be cultured on any of the test media, although it

grew well in immunocompromised nude mice. Thin layer chromatography showed keto-mycolates (similar pattern to *M simiae*); gas chromatography showed tuberculostearic acid and hexadecanoic acid but no evidence of the secondary alcohols characteristic of MAC. In 1992 Bottger *et al*⁴⁸ described 18 patients with AIDS with disseminated mycobacterial infection with a demanding mycobacterium that they named "Mycobacterium genavense". The cultures of blood or tissues grew with difficulty in Bactec 13A vials in 16 patients, but the organism could not be subcultured onto solid media. All samples showed the same unique 16S ribosomal RNA sequence, demonstrating that the organism was a mycobacterium, that it differed from known mycobacterial species and that it was related to *M simiae*.

An organism showing an almost identical sequence was isolated from two patients with AIDS⁴⁹ but, unlike earlier reports, was eventually subcultured onto Middlebrook 7H9 medium with added agar, charcoal and yeast extract after many attempts and after many months' incubation. The authors suggested that prolonged incubation on such media, possibly in an environment with added carbon dioxide, may permit isolation of other fastidious mycobacteria. We have had similar isolates from HIV positive patients and are endeavouring to subculture them; other reference centres are likely to have had similar experiences. Unfortunately, as these organisms have not been reliably subcultured, no information yet exists on their susceptibility to antimycobacterial agents.

The use of the Bactec radiometric technique has permitted the detection of such fastidious mycobacteria in body fluids including blood, although some authors claim that these techniques may underestimate the number of isolates of *M genavense*.⁵⁰

No doubt other fastidious mycobacteria will be isolated, especially in immunocompromised patients. Some of these may be new species, but it should not be forgotten that fastidious strains of common mycobacteria occur. Jackson *et al*⁵¹ documented the isolation of a strain of *M tuberculosis* that would only grow on media deficient in glycerol.

Diagnosis and treatment

On reviewing the literature, it is clear that a large number of mycobacteria have been isolated from patients with AIDS and from HIV negative patients, as well as from environmental sources. In addition to *M tuberculosis* and *M avium* a recent review⁵² lists a total of 21 species associated with HIV infection (table). No doubt other case reports, detailing other mycobacterial isolates, will be published in the future. Also, the use of molecular technologies, and improved isolation methods may lead to the description of new species, as well as re-definition of existing ones. (For example, the recent proposal to divide *M fortuitum* into two species, *M fortuitum sensu stricto* and *M peregrinum*, and *M chelonae* into *M chelonae* and *M abscessus*.⁵³) However, it is important to bear in

Species of mycobacteria associated with HIV infection

<i>Species isolated from patients with AIDS</i>	<i>Species associated with disseminated infection</i>
<i>M fortuitum</i>	<i>M fortuitum</i>
<i>M kansasii</i>	<i>M kansasii</i>
<i>M gordonae</i>	<i>M gordonae</i>
<i>M xenopi</i>	<i>M xenopi</i>
<i>M chelonae</i>	<i>M chelonae</i>
<i>M simiae</i>	<i>M simiae</i>
<i>M haemophilum</i>	<i>M haemophilum</i>
<i>M bovis</i>	
<i>M mageritense</i>	
<i>M scrofulaceum</i>	
<i>M szulgai</i>	
<i>M marinum</i>	
<i>M flavescens</i>	
<i>M asiaticum</i>	

From Pitchenick and Fertel.⁵²

mind that many mycobacteria are present in the environment and may colonise damaged tissues, especially the respiratory tract, without causing clinical infection. The mere isolation of a given species of "atypical mycobacteria" on a single occasion is not necessarily indicative of pathogenicity; this is true even if the patient is immunocompromised. Assessment of the pathogenicity of a given isolate depends on several factors including the site of isolation, number of times isolated, nature of the patient, and previous history. Most important of all is close liaison between clinician and laboratory. The official statement of the American Thoracic Society⁵⁴ gives a detailed review of infections by non-tuberculous mycobacteria as well as criteria for assessing the significance of the isolates. It also gives detailed recommendations for the treatment of these infections, based often on predicted sensitivity patterns. The experience of workers in the United Kingdom is that most atypical mycobacterial species have a range of sensitivity patterns and that combined sensitivity testing using the Bactec method may be necessary to demonstrate synergy between agents which, when tested singly are inactive (Watt, Rayner, Harris, personal observations). As always, good liaison between clinician and laboratory is essential for the management of these often difficult patients.

Newer agents appear to offer promise. The earlier quinolones, especially ciprofloxacin, were shown to possess in vitro activity against many species of mycobacteria⁵⁵⁻⁵⁷ and this was confirmed for other newer compounds.⁵⁸ (Fusidic acid, although showing in vitro activity against *M tuberculosis*, seems to have little activity against other mycobacteria,⁵⁸ and the documented in vitro activity of the phenothiazine chlorpromazine for *M avium* and *M tuberculosis*⁵⁹ has not yet been demonstrated for the lesser known mycobacteria.) In their study of the activity of newer agents against the rapid growers *M fortuitum* and *M chelonae*, Khardori *et al*⁶⁰ showed that *M fortuitum* strains were susceptible to new quinolones, and to new aminoglycosides SCH21420 and SCH22591, but that most *M chelonae* strains were resistant to quinolones, but sensitive to the new aminoglycosides. The newer macrolides, notably clarithromycin and azithromycin, have in vitro activity against many strains of non-tuberculous mycobacteria and have been shown to be active in an animal model⁶¹; roxithromycin

also shows promise.⁶² It must be emphasised that there are few studies that specifically deal with the susceptibility of the lesser known mycobacteria to antimicrobials, and in most documented studies the numbers of strains are small. There are no reports of clinical trials.

Conclusion

Mycobacteria are widely distributed in the environment and therefore it is not surprising that even species normally considered saprophytic have been associated with disease, especially, but not exclusively, in immunocompromised patients. The isolation of any mycobacterial species from blood is likely to be significant, but isolation of mycobacterial species from other sites has to be evaluated on an individual patient basis, involving close liaison between clinician and laboratory. The immune status of the patient, any other underlying medical conditions, the site and frequency of isolation are all factors that need to be taken into consideration. Even then it may be extremely difficult to assess the pathogenicity of a given isolate (for example, repeated isolation of non-tuberculous mycobacteria from the urinary tract of an immunocompetent patient with no evidence of renal disease). Yet it is important to do so before considering starting therapy; there are very few agreed regimens for the treatment of infections due to the lesser known mycobacteria and the patient may require treatment for many months. The criteria of significance should be just as strict in HIV positive patients. Also, it is important that laboratories incubate cultures for mycobacteria for a full 12 weeks, rather than discarding them routinely at six weeks.

There is much work still to be done on the pathogenicity and susceptibility of these interesting organisms and proper clinical trials (probably multicentre) are an urgent necessity.

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